Drugs of the Future 2006, 31(5): 379-384

CCC: 0377-8282/2006
DOI: 10.1358/dof.2006.031.05.996549

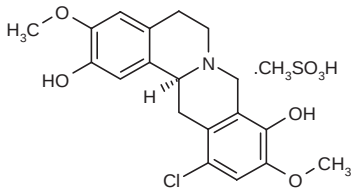
l-Chloroscoulerine Mesylate

Antipsychotic
Dopamine D1 Agonist/D2 Antagonist

l-THPB-18 Methanesulfonate
l-CSL Methanesulfonate

(*S*)-2,9-Dihydroxy-3,10-dimethoxy-12-chlorotetrahydroprotoberberine methanesulfonate

(*S*)-12-Chloro-5,8,13,13a-tetrahydro-3,10-dimethoxy-6*H*-dibenzo[*a,g*]quinolizine-2,9-diol methanesulfonate



$C_{19}H_{20}ClNO_4.CH_4O_3S$
Mol wt: 457.9258

CAS: 873841-24-8

CAS: 174364-37-5 (as free base)

CAS: 175280-76-9 (as [*R*]-isomer free base)

CAS: 17891-00-8 (as racemate free base)

EN: 291311

Abstract

The novel dopamine ligand *l*-chloroscoulerine (*l*-CSL) mesylate is under development for the treatment of schizophrenia. *l*-CSL, a derivative of tetrahydroprotoberberine, is structurally different from all known antipsychotic drugs. *l*-CSL shows high affinity for D1 receptors and moderate affinity for D2 receptors in receptor binding assays. In electrophysiological studies, it exhibits dual action as a D1 agonist and a D2 antagonist, a profile considered to represent a new strategy for treating schizophrenia. Behavioral experiments also demonstrate that *l*-CSL is beneficial against negative symptoms. Moreover, the compound from which *l*-CSL is derived, *l*-stepholidine, showed favorable activity and few side effects in the treatment of schizophrenia in clinical trials. *l*-CSL is more potent than *l*-stepholidine and displays low toxicity. The efficacy of *l*-CSL for schizophrenia therefore merits further investigation.

Synthesis

l-Chloroscoulerine mesylate can be prepared from isovanillin by several different ways (Scheme 1):

1) The starting material isovanillin (I) is treated with KCN, followed by reduction and hydrolysis with $SnCl_2$ in acid to provide 3-hydroxy-4-methoxybenzeneacetic acid (II). Compound (II) is chlorinated with SO_2Cl_2 in HAc to afford 2-chloro-5-hydroxy-4-methoxyphenylacetic acid (IIIa), which is fused with 4-benzyloxy-3-methoxyphenethylamine (IV) by heating at 180 ºC to give *N*-(4-benzyloxy-3-methoxyphenethyl)-2-(2-chloro-5-hydroxy-4-methoxyphenyl)acetamide (Va). Acetylation of compound (Va) with Ac_2O gives the corresponding 5-acetyl derivative, which is then treated with $POCl_3$ by Bischler-Napieralski reaction to provide the 3,4-dihydroisoquinoline derivative (VIa). Compound (VIa) is reduced and deprotected with $NaBH_4$ to give the corresponding tetrahydroisoquinoline (VIIa). The Mannich reaction of compound (VIIa) with formaldehyde affords racemic 2-benzoxyl-3,10-dimethoxy-9-hydroxy-12-chlorotetrahydroberberine (VIII), which is optically resolved to give the levoisomer (*l*-VIII) (1, 2). Finally, compound (*l*-VIII) is hydrogenated by means of a catalyst to provide *l*-chloroscoulerine (*l*-IX), which is treated with methanesulfonic acid to yield the desired *l*-chloroscoulerine mesylate (2).

2) Treatment of isovanillin (I) with benzyl chloride, followed by chlorination with chlorine, gives 5-benzyloxy-2-chloro-4-methoxybenzaldehyde (X), which is oxidized by Ag_2O to provide the corresponding benzoic acid derivative (XI). From compound (XI), the corresponding benzeneacetic acid derivative (IIIb) is obtained through an Arndt-Eistert reaction: chlorination of compound (XI) with $SOCl_2$ by heating under reflux, followed by reaction with diazomethane, gives 5-benzyloxy-2-chloro-4-methoxy-ω-diazoacetophenone (XII). Compound (XII) is treated with Ag_2O, followed by hydrolyzation with methanol, to afford methyl 5-benzyloxy-2-chloro-4-methoxyphenylacetate (IIIb). The ester (IIIb) and 4-benzyloxy-3-methoxyphenethylamine (IV) are condensed at high temperature under N_2 to give the acetamide derivative (Vb). Bischler-Napieralski cyclization of the amide with $POCl_3$ then provides the 3,4-dihydroisoquinoline (VIb). Reduction of compound (VIb) with $NaBH_4$ gives 1,2,3,4-tetrahydroiso-

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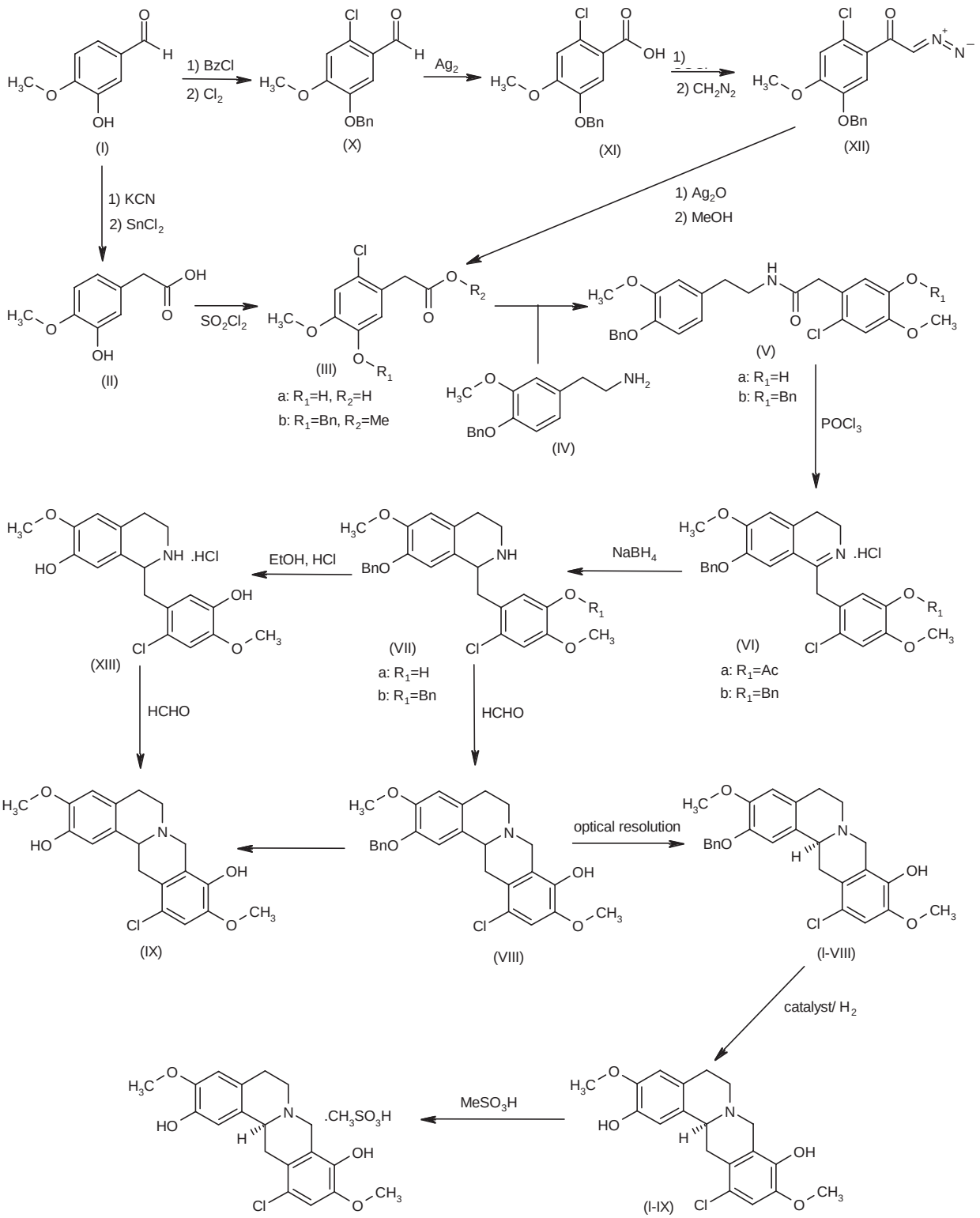
Scheme 1: Synthesis of *l*-Chloroscoulerine Mesylate



quinoline (VIIb). Debenzylation of compound (VIIb) with concentrated hydrochloride affords the phenolic base (XIII), which is cyclized with formaldehyde by a Mannich reaction to give racemic chloroscoulerine (IX) (3).

Background

Based on the "hyperdopaminergic hypothesis of schizophrenia", typical antipsychotics are dopamine (DA) D2 antagonists. They have effects on positive symptoms of schizophrenia, but are less effective against negative symptoms, and the serious extrapyramidal side effects associated with DA antagonism limited the clinical use of these agents. The atypical antipsychotics possessing D2- and 5-HT_{2A}-antagonist effects are beneficial against both positive and negative symptoms, although no significant effect is seen on cognitive impairment.

Recently, the pathogenesis of schizophrenia has been suggested to involve dysfunction of dopamine D1 receptors in the medial prefrontal cortex (mPFC), which results in dopamine D2 receptor hyperactivity in subcortical regions such as the ventral tegmental area (VTA) and the nucleus accumbens (NAc). Dopamine D1 receptor dysfunction is involved in the negative symptoms of schizophrenia, whereas D2 receptor hyperactivity results in the positive symptoms of this disorder (4-6). According to this new hypothesis, an effective antipsychotic drug should have both D1 receptor-agonist and D2 receptor-antagonist actions. *l*-Stepholidine (*l*-SPD) is an active ingredient of the Chinese herb *Stephania* with such a profile of activity (7, 8).

From pharmacological studies of the Chinese medicine *Corydalis yanhusuo*, Jin *et al*. found that tetrahydroprotoberberines (THPBs) isolated from *C. yanhusuo* are a new type of DA antagonists. Among the analogues, *l*-SPD showed the highest affinity for dopamine D1 and D2 receptors (9-13), whereas it displayed only moderate or low affinity for 5-HT_2 receptors and α_2-adrenoceptors, and little or no affinity for other transmitter receptors (14, 15). Three-dimensional QSAR studies (16-19) of the interaction of THPBs with DA receptors were also carried out, and the results confirmed affinity for D1 and D2 receptors.

l-SPD was initially considered a DA receptor antagonist. In normal and reserpinized rats, it showed antagonist effects at D1 and D2 receptors (9, 10, 20). However, in 6-hydroxydopamine (6-OHDA)-lesioned rats, it displayed agonist and antagonist effects on rotational behavior (15, 21). Further studies have indicated that *l*-SPD possesses dual actions as a D1 receptor agonist and D2 receptor antagonist. These dual actions have also been demonstrated in receptor binding (13, 22), biochemical and immunohistochemical (23-25), electrophysiological (26-28) and behavioral studies (29-31). Importantly, the dual actions of *l*-SPD have been detected in both mPFC and subcortical structures, including NAc, VTA and basal ganglia dopamine systems. This characteristic is consistent with the new theory of the pathogenesis of schizophrenia mentioned above. Thus, *l*-SPD may be beneficial for the treatment of schizophrenia (7).

In preliminary double-blind clinical trials, *l*-SPD was demonstrated to be effective in schizophrenia, especially in treating the negative symptoms. The efficacy of *l*-SPD was superior to perphenazine and similar to sulpiride and clozapine (32-35). Moreover, *l*-SPD induced no extrapyramidal symptoms (32-35) and markedly reduced the tardive dyskinesia associated with typical antipsychotic drugs (36). From these results, it was suggested that the clinical activity of *l*-SPD is consistent with its dual pharmacological actions. The D1 receptor-agonist effect of *l*-SPD on the mPFC is effective in improving negative symptoms, whereas its D2 receptor-antagonist effect on the subcortex results in beneficial effects on positive symptoms.

In order to develop new antipsychotic drugs with greater efficacy and fewer undesirable side effects, a series of THPBs was examined and *l*-chloroscoulerine (*l*-CSL), a derivative of *l*-SPD with more potent activity at DA receptors, was selected as a good candidate for a novel antipsychotic agent with dual D1-agonist and D2-antagonist properties. The chemical structure of *l*-CSL is completely different from all the currently known antipsychotics, such as haloperidol, risperidone, olanzapine and aripiprazole (8).

Preclinical Pharmacology

In competitive receptor binding assays using calf striatum (37, 38), *l*-CSL showed high affinity for D1 receptors and moderate affinity for D2 receptors, with the highest affinity among THPBs. For the D1 receptor expressed in Sf9 cells (39, 40), the affinity of *l*-CSL was generally consistent with previous results from calf striatal tissues (Table I). In this assay, *l*-CSL increased intracellular cAMP levels in a concentration-dependent manner, with an EC_{50} value of 0.72 μmol/l, which indicated that it has D1 receptor-agonist activity at the cellular-molecular level (39). 3D-QSAR studies also demonstrated the high affinity of *l*-CSL for D1 and D2 receptors (18, 19).

In a two-site model program analysis, CSL exhibited two binding sites (R_H and R_L) on D1 receptors and one binding site on D2 receptors. These studies demonstrat-

Table I: K_i values of l-SPD and CSL racemate and enantiomers for binding to dopamine receptors (38-40).

K_i (nmol/l)	Calf striatum		Sf9 cells	
	D1	D2	D1	D2
l-SPD	8.6	80	11	350
l-CSL	5.7	5.7	6.3	870
dl-CSL	8.9	9.6	—-	—-
d-CSL	135	9150	—-	—-

ed that CSL possessed both D1-agonist and D2-antagonist properties (22).

In rat striatum, CSL (40 mg/kg) increased levodopa accumulation and completely reversed apomorphine inhibition of levodopa content. In electrophysiological tests, CSL (80 μg/kg i.v.) attenuated the inhibition by apomorphine (15 μg/kg i.v.) of substantia nigra pars compacta (SNC) DA cell firing rate and restored the firing activity to pretreatment levels. Thus, CSL showed antagonist activity at D2 autoreceptors (41).

The potency of *l*-CSL on the firing of SNc DA neurons was studied in rats. In normal rats, *l*-CSL attenuated apomorphine (10 μg/kg i.v.)-induced inhibition of DA cell firing, with an ED_{50} of 7.8 μg/kg. In reserpinized rats, *l*-CSL blocked the inhibition caused by SKF-38393 (4 mg/kg i.v.), with an ED_{50} value of 0.51 mg/kg. *l*-CSL showed mixed D1/D2-antagonist effects, being more potent than *l*-SPD (42).

The action of *l*-CSL on DA receptors in the VTA-mPFC-NAc system, which is implicated in the pathogenesis of schizophrenia, was studied. In gallamine-paralyzed rats, *l*-CSL attenuated the apomorphine (20 μg/kg)-induced inhibition of VTA DA cell firing activity, with an ED_{50} value of 66 μg/kg. These results demonstrated that *l*-CSL was a D2 receptor antagonist on VTA DA neurons (43). Another electrophysiological study was carried out in NAc neurons of unilateral 6-OHDA-lesioned rats. The results indicated that *l*-CSL can elicit a biphasic firing response of NAc neurons and possesses dual D1-agonist/D2-antagonist actions in the VTA-NAc DA system, which is similar to that of *l*-SPD (44). The D1-agonist action of the antipsychotic on mPFC neurons associated with the D2-antagonist action in subcortical NAc is very consistent with the new strategy for antipsychotic research.

In behavioral experiments, all the enantiomers of CSL showed an effect on DA receptors, the *l*-enantiomer being the most potent. *l*-CSL at doses of 5-40 mg/kg inhibited the stereotypy induced by apomorphine in rats, and at doses of 5-80 mg/kg it induced transient catalepsy. Furthermore, *l*-CSL (10-60 mg/kg) inhibited jumping behavior induced by amphetamine plus levodopa in mice. *l*-CSL also antagonized the spontaneous locomotor activity of normal and amphetamine-treated mice at doses of 10-80 mg/kg. These results suggest that *l*-CSL has an antagonist effect on DA receptors. However, in 6-OHDA-lesioned rats, *l*-CSL exhibited agonist effects on D1 receptors. Overall, it appears that *l*-CSL has dual actions at DA receptors and its effects were similar to those of *l*-SPD (1, 37, 38).

The effect of *l*-CSL on morphine-induced conditioned place preference was investigated in mice. It was demonstrated that *l*-CSL suppresses the development of place preference by blocking D2 receptors (45).

The pharmacological properties of *l*-CSL methanesulfonate were studied in comparison with those of olanzapine in the forced swimming test. In the amphetamine swimming normalization test in mice, intragastric *l*-CSL methanesulfonate inhibited the effect of amphetamine in a dose-dependent manner, with an ED_{50} of 11.6 mg/kg compared to a value of 0.22 mg/kg for olanzapine. However, in the phencyclidine (PCP)-induced immobility test in mice, *l*-CSL methanesulfonate attenuated the enhancement of immobility (ED_{50} = 10.9 mg/kg) with a potency similar to that of olanzapine (2). Similarly, in the PCP-induced immobility test in rats, the ED_{50} values for *l*-CSL methanesulfonate and olanzapine were 7.0 and 6.2 mg/kg, respectively (46).

Taken together, results from *in vitro* and *in vivo* studies have demonstrated that *l*-CSL methanesulfonate has a dual effect as a D1 agonist/D2 antagonist and is more potent than *l*-SPD. Thus, *l*-CSL methanesulfonate may be an effective agent for the treatment of schizophrenia with reduced adverse effects compared to current clinically available agents. In particular, its additional potent D1 agonism suggests that it may have beneficial effects on negative symptoms.

Pharmacokinetics

In preliminary pharmacokinetic studies in rats, *l*-CSL methanesulfonate was well absorbed. In SD rats given a dose of 35 mg/kg i.g., *l*-CSL methanesulfonate was distributed to various tissues in relatively high concentrations compared to plasma. In particular, the concentrations in cortex and thalamus were 20 times higher than in plasma, suggesting that it was delivered to the brain (46).

In vitro tests in Caco-2 cell monolayers demonstrated permeability of *l*-CSL, which suggests that this compound can readily cross the blood-brain barrier (46).

Safety

The single-dose toxicity of i.v. and i.g. *l*-CSL methanesulfonate was assessed in mice and rats. The acute LD_{50} of *l*-CSL methanesulfonate in mice was 120 mg/kg i.v. and 538 mg/kg i.g. In rats, the respective LD_{50} values were 90.5 and > 800 mg/kg.

In reproductive and developmental toxicity studies, *l*-CSL methanesulfonate was administered orally to pregnant rats at doses of 30, 100 and 300 mg/kg/day. No significant change in clinical signs or food consumption was observed during pregnancy. In the highest dose group, the weight of the uterus was less than in the other groups. Dose-dependent decreases in the weight of liver and spleen were also seen. Moreover, the number of implantations, live embryos and fetusus was also decreased with increasing doses. The maximum no-adverse-effect dose was estimated to be 100 mg/kg for pregnant rats and fetuses.

In preliminary chronic toxicity studies, *l*-CSL methanesulfonate was given orally to rats at doses of 30, 100 and 300 mg/kg/day for 30 days. No significant changes were observed in clinical signs, hematological analysis, blood biochemistry and anatomical examination. In another study, beagle dogs were given oral doses of 10, 30 and 100 mg/kg/day for 6 weeks. Animals in the 30 and 100 mg/kg groups showed some slight neuronal symptoms, but no other changes were seen in any group.

In the bacterial reverse mutation assay, *l*-CSL methanesulfonate had no genotoxic effects on *Salmonella typhimurium* at 5-5000 μg/plate. In the chromosomal aberration test in Chinese hamster lung (CHL) cells, with or without S9, the results were negative. In the ICR mouse bone cell marrow micronucleus test, *l*-CSL methanesulfonate had no effect on the formation of polychromatic erythrocytes. These studies indicate that *l*-CSL methanesulfonate has no mutagenic activity (46).

Source

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